REMARKS

Claims Rejection - 35 U.S.C. 112 1st

Claims 49-57 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the enablement requirement.

The rejection particularly contends, starting at page 7, that if one were to detect expression of CDCA1 in blood that is different from healthy patients, it would be unpredictable if this difference is due to the presence of rheumatoid arthritis or to some other disease or condition, such as SLE, on the grounds that Pascual *et al.* teaches that CDCA1 is a gene that is down-regulated in SLE patients likely to progress to renal disease, as indicated at "*Table 1A, ¶0133 and throughout*".

Applicant respectfully traverses this contention on the grounds that this reference clearly does not provide any data relating to differences in expression of this gene between healthy subjects and either SLE patients likely to progress to renal disease, or SLE patients not likely to progress to renal disease. Firstly, Table 1A does not in fact appear to provide any data relating to CDCA1 gene expression. The only data relating to CDCA1 expression set forth by Pascual *et al.* appears to be provided by Table 1B which sets forth a list of genes which are putatively up-regulated in SLE patients who are likely to progress to renal involvement relative to SLE patients which are not likely to progress to renal involvement. The fact that Table 1B only relates to differential CDCA1 gene expression between different groups of SLE patients, and does not relate in any way to expression levels in healthy subjects is clearly evident at paragraph [0059] which states that the genes set forth in Table 1B "*...were identified by monitoring the expression of these genes in SLE patients over the course of approximately 3 years, and comparing the expression over this time period in patients that progressed to renal involvement to the expression in those patients who did not progress to renal involvement.*" Applicant would moreover point out that the genes which were found by Pascual *et al.* to be differentially expressed between healthy control subjects and SLE patients are set forth in Tables 2A and 2B, in accordance with the recitations: "*The inventors have broadened these studies*

of differential gene expression in SLE patients as compared to controls, and list 3004 SLE-associated genes in Tables 2A and 2B. Table 2A lists 1,751 genes that are down-regulated in SLE patients by at least one-fold as compared to the control, while Table 2B lists 1,253 genes that are up-regulated in SLE patients by at least one-fold as compared to controls." (paragraph [0070]); and "*The 3004 transcripts disclosed herein were identified as being differentially expressed by statistical comparisons between the healthy and SLE groups...*" (paragraph [0047]). Applicant points out that neither Table 2A nor Table 2B appears to refer to CDCA1. As such, Applicant respectfully submits that the gene expression data disclosed in Pascual *et al.* in fact can clearly only be arguably interpreted as teaching, in diametric contrast to the rejection's contention, that CDCA1 is not differentially expressed in blood between SLE patients and healthy control subjects.

Moreover, Applicant respectfully submits that, as well as failing to indicate that CDCA1 is differentially expressed in blood between SLE patients and healthy control subjects, the data set forth by Pascual *et al.* relating to differential gene expression between such subjects (Tables 2A and 2B) is in fact in any case drawn to subject matter which is not encompassed by the claims. Namely, the data set forth by Pascual *et al.* only relates to genes which are differently expressed in peripheral blood mononuclear cells (PBMCs or "mononuclear cells" ; i.e. lymphocytes and monocytes), hence in leukocytes which are fractionated into cell types. This is clearly evidenced, for example, in the materials and methods section of Pascual *et al.* describing RNA sample isolation, in accordance with the recitation: "*Blood leukocytes were isolated on Ficoll gradient...*" (paragraph [0127]). It is well understood in the art that such Ficoll fractionation is employed to isolate PBMCs from granulocytes (refer, for example, to Fig. A.23. Immunobiology. Garland Publishing. 2001. Fifth Edition. Janeway, Travers, Walport, and Shlomchik, eds., of record), granulocytes being the majority cell component of leukocytes (refer, for example, to enclosed Complete Blood Count (CBC) table. Merck Manual Home Edition, 2006). In relevant contrast, the claims are drawn to RNA of samples which comprise unfractionated leukocytes, i.e. which comprise granulocytes as well as the minority mononuclear cell fraction of leukocytes. Thus, in setting forth data relating only to genes which are differentially expressed in a minority fraction of

leukocytes, Pascual *et al.* fails to provide teachings relating to genes which are globally differentially expressed in unfractionated leukocytes, as required by the claims. Namely, unfractionated leukocytes further comprise a majority fraction of granulocytes which are a distinct cell type relative to mononuclear cells and which inherently have distinct gene expression profiles relative to mononuclear cells [refer, for example to enclosed abstract of Hashimoto S. et al., 2003. Gene expression profile in human leukocytes. Blood 101:3509-13; and to Figure 5C of the instant specification which indicates significantly different expression levels of an exemplary gene between granulocytes ("G.R.") and mononuclear cells, the latter being represented by cumulative levels of the combination of B-lymphocytes ("CD19"), T-lymphocytes ("CD3") and monocytes ("MONO")]. Thus, it cannot be predictably extrapolated that the global differential expression of any given gene (such as CDCA1 between healthy control subjects and SLE patients) observed in Ficoll-fractionated mononuclear cells, as taught by Pascual *et al.*, will also be observed in unfractionated leukocytes, as required by the claims.

As such the teachings of Pascual *et al.* do not teach that the field of the invention is highly unpredictable, and cannot be used as grounds for contending that the claims are not enabled.

As such the Applicants believe that the art is sufficiently predictable such that the amount of experimentation to perform the instantly claimed methods of diagnosing rheumatoid arthritis and identifying candidate subjects who may have rheumatoid arthritis is not undue. In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejections.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: Nov 30, 2007

Amy DeCloux 54849 for

Name: Kathleen M. Williams
Registration No.: 34,380
Customer No.: 21874
Edwards Angell Palmer & Dodge LLP
P.O. Box 55874
Boston, MA 02205
Tel: 617-239-0100

Encl.:

Abstract of Hashimoto S. et al., 2003. Gene expression profile in human leukocytes. Blood 101:3509-13; and

Complete Blood Count (CBC) table. Merck Manual Home Edition, 2006.